

In re Application of: Chaim GILON et al.
Serial No.: 10/508,959
Filed: August 16, 2005
Office Action Mailing Date: October 16, 2007

Examiner: Desai, Anand U.
Group Art Unit: 1656
Attorney Docket: 28557

In the Claims:

1. (Withdrawn) A conjugate comprising a histone moiety covalently linked to a macromolecule-of-interest, said histone moiety being transportable through cell membranes and importable into cell nuclei.
2. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest has therapeutic activity.
3. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest is a non-marker macromolecule.
4. (Withdrawn) The conjugate of claim 1, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.
5. (Withdrawn) The conjugate of claim 1, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.
6. (Withdrawn) The conjugate of claim 1, wherein said histone moiety comprises H2A.
7. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest is a chemically synthesized macromolecule.
8. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest is isolated from a biological source.

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9. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest is a protein.

10. (Withdrawn) The conjugate of claim 1, wherein said macromolecule-of-interest is a nucleic acid.

11. (Withdrawn) The conjugate of claim 10, wherein said nucleic acid is an oligonucleotide.

12. (Withdrawn) The conjugate of claim 10, wherein said nucleic acid is a DNA.

13. (Withdrawn) The conjugate of claim 10, wherein said nucleic acid is an RNA.

14. (Withdrawn) The conjugate of claim 10, wherein said nucleic acid encodes for a gene.

15. (Withdrawn) The conjugate of claim 1, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a spacer.

16. (Withdrawn) The conjugate of claim 15, wherein said spacer comprises a sulfide bond.

17. (Withdrawn) The conjugate of claim 1, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a non-peptide bond.

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18. (Withdrawn) A polynucleotide encoding an in-frame polypeptide conjugate, said polypeptide conjugate comprises a histone moiety and a protein-of-interest, said histone moiety being transportable through cell membranes and importable into cell nuclei.

19. (Withdrawn) The polynucleotide of claim 18, wherein said protein-of-interest has therapeutic activity.

20. (Withdrawn) The polynucleotide of claim 18, wherein said protein-of-interest is a non-marker protein.

21. (Withdrawn) The polynucleotide of claim 18, wherein said histone moiety is selected from the group consisting of H1, H2A, H2B, H3 and H4.

22. (Withdrawn) The polynucleotide of claim 18, wherein said histone moiety comprises H2A.

23. (Withdrawn) A nucleic acid construct, comprising the polynucleotide of claim 18.

24. (Withdrawn) The nucleic acid construct of claim 23, further comprising a cis-acting regulatory element.

25. (Withdrawn) A pharmaceutical composition comprising, as an active ingredient, the conjugate of claim 1 and a pharmaceutically acceptable carrier.

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26. (Withdrawn) The pharmaceutical composition of claim 25, identified for use in the treatment of a proliferative disorder or disease, a genetic disorder or disease, a bacterial infection or a viral infection.

27. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest has therapeutic activity.

28. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest is a non-marker macromolecule.

29. (Withdrawn) The pharmaceutical composition of claim 25, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.

30. (Withdrawn) The pharmaceutical composition of claim 25, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

31. (Withdrawn) The pharmaceutical composition of claim 25, wherein said histone moiety comprises H2A.

32. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest is a chemically synthesized macromolecule.

33. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest is isolated from a biological source.

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34. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest is a protein.

35. (Withdrawn) The pharmaceutical composition of claim 25, wherein said macromolecule-of-interest is a nucleic acid.

36. (Withdrawn) The pharmaceutical composition of claim 35, wherein said nucleic acid is an oligonucleotide.

37. (Withdrawn) The pharmaceutical composition of claim 35, wherein said nucleic acid is a DNA.

38. (Withdrawn) The pharmaceutical composition of claim 35, wherein said nucleic acid is an RNA.

39. (Withdrawn) The pharmaceutical composition of claim 35, wherein said nucleic acid encodes for a gene.

40. (Withdrawn) The pharmaceutical composition of claim 25, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a spacer.

41. (Withdrawn) The pharmaceutical composition of claim 40, wherein said spacer comprises a sulfide bond.

42. (Withdrawn) The pharmaceutical composition of claim 25, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a non-peptide bond.

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43. (Withdrawn) A method of synthesizing the conjugate of claim 1, the method comprising covalently linking said histone moiety and said macromolecule-of-interest, to thereby produce said conjugate.

44. (Withdrawn) The method of claim 43, further comprising, prior to said covalently linking, covalently attaching a spacer to said macromolecule-of-interest.

45. (Withdrawn) The method of claim 43, further comprising, prior to said covalently linking, covalently attaching a spacer to said histone moiety.

46. (Withdrawn) The method of claim 44, further comprising, prior to said covalently linking, functionalizing said histone moiety into a functionalized derivative which comprises a free functional group.

47. (Withdrawn) The method of claim 46, wherein covalently linking said histone moiety and said macromolecule-of-interest comprises covalently attaching said functional group to said spacer.

48. (Withdrawn) The method of claim 46, wherein said functionalized derivative is a thiolated derivative and said functional group is a thiol group.

49. (Withdrawn) The method of claim 45, further comprising, prior to said covalently linking, functionalizing said macromolecule-of-interest into a functionalized derivative which comprises a free functional group.

50. (Withdrawn) The method of claim 49, wherein said functionalized derivative is a thiolated derivative and said functional group is a thiol group.

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51. (Withdrawn) The method of claim 49, wherein covalently linking said histone moiety and said macromolecule-of-interest comprises covalently attaching said functional group to said spacer.

52. (Withdrawn) The method of claim 43, wherein said covalently linking is performed using a cross-linking agent.

53. (Withdrawn) The method of claim 52, wherein said cross-linking agent is Sulfo-SMMC.

54. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest has therapeutic activity.

55. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest is a non-marker macromolecule.

56. (Withdrawn) The method of claim 43, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.

57. (Withdrawn) The method of claim 43, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

58. (Withdrawn) The method of claim 43, wherein said histone moiety comprises H2A.

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59. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest is a chemically synthesized macromolecule.

60. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest is isolated from a biological source.

61. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest is a protein.

62. (Withdrawn) The method of claim 43, wherein said macromolecule-of-interest is a nucleic acid.

63. (Withdrawn) The method of claim 62, wherein said nucleic acid is an oligonucleotide.

64. (Withdrawn) The method of claim 62, wherein said nucleic acid is a DNA.

65. (Withdrawn) The method of claim 62, wherein said nucleic acid is an RNA.

66. (Withdrawn) The method of claim 62, wherein said nucleic acid encodes for a gene.

67. (Withdrawn) The method of claim 43, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a spacer.

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68. (Withdrawn) The method of claim 67, wherein said spacer comprises a sulfide bond.

69. (Currently amended) A method of delivering a macromolecule-of-interest into a cell, the method comprising ~~co-incubating~~contacting the cell with a conjugate comprising a histone moiety covalently linked to said macromolecule-of-interest, said histone moiety being transportable through cell membranes and importable into cell nuclei, and is being selected from the group consisting of at least one histone protein and at least one peptide sequence derived from a histone protein, said peptide sequence comprises a positively charged amino acid sequence and a nuclear localization signal. ~~the conjugate of claim 1.~~

70. (Canceled)

71. (Original) The method of claim 69, wherein said macromolecule-of-interest has therapeutic activity.

72. (Original) The method of claim 69, wherein said macromolecule-of-interest is a non-marker macromolecule.

73. (Canceled)

74. (Original) The method of claim 69, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

75. (Original) The method of claim 69, wherein said at least one histone moiety comprises H2A.

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76. (Original) The method of claim 69, wherein said macromolecule-of-interest is a chemically synthesized macromolecule.

77. (Original) The method of claim 69, wherein said macromolecule-of-interest is isolated from a biological source.

78. (Original) The method of claim 69, wherein said macromolecule-of-interest is a protein.

79. (Withdrawn) The method of claim 69, wherein said macromolecule-of-interest is a nucleic acid.

80. (Withdrawn) The method of claim 79, wherein said nucleic acid is an oligonucleotide.

81. (Withdrawn) The method of claim 79, wherein said nucleic acid is a DNA.

82. (Withdrawn) The method of claim 79, wherein said nucleic acid is an RNA.

83. (Withdrawn) The method of claim 79, wherein said nucleic acid encodes for a gene.

84. (Original) The method of claim 69, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a spacer.

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85. (Original) The method of claim 84, wherein said spacer comprises a sulfide bond.

86. (Original) The method of claim 69, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a non-peptide bond.

87. (Withdrawn) A method of treating a proliferative disorder or disease, a genetic disorder or disease, a bacterial infection and/or a viral infection in a subject in need thereof, the method comprising administering to the subject a therapeutically effective amount of the conjugate of claim 1, wherein said macromolecule-of-interest has a therapeutic activity in treating said proliferative disorder or disease, said genetic disorder or disease, said bacterial infection and/or said viral infection.

88. (Withdrawn) The method of claim 87, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.

89. (Withdrawn) The method of claim 87, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

90. (Withdrawn) The method of claim 87, wherein said at least one histone moiety comprises H2A.

91. (Withdrawn) The method of claim 87, wherein said macromolecule-of-interest is a chemically synthesized macromolecule.

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92. (Withdrawn) The method of claim 87, wherein said macromolecule-of-interest is isolated from a biological source.

93. (Withdrawn) The method of claim 87, wherein said macromolecule-of-interest is a protein.

94. (Withdrawn) The method of claim 87, wherein said macromolecule-of-interest is a nucleic acid.

95. (Withdrawn) The method of claim 94, wherein said nucleic acid is an oligonucleotide.

96. (Withdrawn) The method of claim 94, wherein said nucleic acid is a DNA.

97. (Withdrawn) The method of claim 94, wherein said nucleic acid is an RNA.

98. (Withdrawn) The method of claim 94, wherein said nucleic acid encodes for a gene.

99. (Withdrawn) The method of claim 87, wherein said histone moiety is covalently linked to said macromolecule-of-interest via a spacer.

100. (Withdrawn) The method of claim 99, wherein said spacer comprises a sulfide bond.

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101. (Withdrawn) The method of claim 87, wherein said histone moiety is covalently linked to said macromolecule of interest via a non-peptide bond.

102. (Withdrawn) A method of quantitatively determining a nuclear uptake and/or a cytoplasmic uptake of a moiety into cells, the method comprising:

contacting said moiety with said cells;

fractionating said cells into a cytoplasmic fraction and a nuclei fraction; and

quantitatively determining an amount or concentration of said moiety in said cytoplasmic fraction and in said nuclei fraction, thereby quantitatively determining the nuclear uptake and/or the cytoplasmic uptake of the moiety into the cells.

103. (Withdrawn) The method of claim 102, wherein said contacting is performed by co-incubating said cells and said moiety.

104. (Withdrawn) The method of claim 102, wherein said fractionating is performed by permeabilizing the plasma membrane of said cells, to thereby obtain said cytoplasmic fraction and thereafter permeabilizing the nuclear membrane of said cells, to thereby obtain said nuclei fraction.

105. (Withdrawn) The method of claim 102, wherein said quantitatively determining comprises:

contacting said cytoplasmic fraction or said nuclei fraction with a solid phase having binding affinity to said moiety, to thereby adhere said moiety to said solid phase;

affinity attaching a detectable molecule to said moiety; and

quantitatively detecting an amount or concentration of said detectable molecule affinity bound to said moiety, to thereby quantitatively determining the

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amount or concentration of said moiety in said cytoplasmic fraction or in said nuclei fraction.

106. (Withdrawn) The method of claim 105, wherein said solid phase is selected from the group consisting of a microtiter plate, a chip and a glass.

107. (Withdrawn) The method of claim 105, wherein said detectable molecule comprises an enzyme capable of catalyzing a colorimetric reaction, a bead, a pigment and a fluorophore.

108. (Withdrawn) The method of claim 102, wherein said moiety includes a detection group attached thereto.

109. (Withdrawn) The method of claim 108, wherein said detection group is biotin.

110. (Withdrawn) The method of claim 102, wherein said moiety is a macromolecule.

111. (Withdrawn) The method of claim 110, wherein said macromolecule is a protein.

112. (Withdrawn) The method of claim 110, wherein said macromolecule is a nucleic acid.

113. (Withdrawn) The method of claim 110, wherein said macromolecule is a histone moiety.

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114. (Withdrawn) The method of claim 113, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.

115. (Withdrawn) The method of claim 113, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

116. (Withdrawn) The method of claim 113, wherein said histone moiety comprises H2A.

117. (Withdrawn) The method of claim 110, wherein said macromolecule is a chemically synthesized macromolecule.

118. (Withdrawn) The method of claim 110, wherein said macromolecule is isolated from a biological source.

119. (Withdrawn) The method of claim 112, wherein said nucleic acid is an oligonucleotide.

120. (Withdrawn) The method of claim 112, wherein said nucleic acid is a DNA.

121. (Withdrawn) The method of claim 112, wherein said nucleic acid is an RNA.

122. (Withdrawn) The method of claim 112, wherein said nucleic acid encodes for a gene.

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123. (Withdrawn) The method of claim 102, wherein said moiety is a conjugate of a first macromolecule covalently attached to a second macromolecule.

124. (Withdrawn) The method of claim 123, wherein said first macromolecule is a histone moiety and said second macromolecule is selected from the group consisting of a protein and a nucleic acid.

125. (Withdrawn) The method of claim 124, wherein said histone moiety is selected from the group consisting of at least one histone protein and at least one derivative of a histone protein.

126. (Withdrawn) The method of claim 124, wherein said histone moiety comprises a mixture of at least two histone proteins selected from the group consisting of H1, H2A, H2B, H3 and H4.

127. (Withdrawn) The method of claim 124, wherein said histone moiety comprises H2A.

128. (Withdrawn) The method of claim 124, wherein said nucleic acid is an oligonucleotide.

129. (Withdrawn) The method of claim 124, wherein said nucleic acid is a DNA.

130. (Withdrawn) The method of claim 124, wherein said nucleic acid is an RNA.

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131. (Withdrawn) The method of claim 124, wherein said nucleic acid encodes for a gene.